Recent Reverses in Immunisation

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Diphtheria immunisation has been criticised recently on two counts. First, as one type of trauma to muscle which may influence the site of paralysis in persons incubating poliomyelitis; and second, on its failure to restrict epidemic spread of the gravis strain of diphtheria bacillus.

Evidence of an association between the site of a previous inoculation and the site of paralysis in poliomyelitis is contained in reports from Melbourne (McCloskey), and London (Geffen), and in the statistical survey of certain areas in England by Hill and Knowelden. These reports state that children inoculated within four weeks prior to the onset of poliomyelitis have developed paralysis of the arms more often than non-inoculated children. This finding has not been confirmed in Cardiff or in Belfast. A report of the 1950 epidemic in Belfast, in which the *non*-inoculated children show an unusually high proportion of arm paralysis, has been published in the *British Medical Journal*. Geffen, in London, calculates the risk of association, site of paralysis with site of inoculation, using the combined diphtheria-pertussis antigen to be 1 in 1,800 inoculations, while, in Belfast, using a pure diphtheria toxoid (P.T.A.P.), we failed to find any such association in 6,250 inoculations. This difference may be due to the use of different antigens.

The responsibility of advising the cessation of immunisation during an epidemic of poliomyelitis is a heavy one, and should rest on the Medical Officer of Health of the affected area. This was pointed out by the Ministry of Health in England during the 1950 epidemic. Certainly the Medical Officer of Health should be in a position to assess the relative risk of diphtheria in the non-immunised and arm paralysis in the recently immunised. There is no shadow of doubt that the former is by far the greater risk in Belfast.

A recent M.R.C. report describes outbreaks of diphtheria, mainly of the gravis type, in Dundee and on Tyneside, in which immunisation failed to prevent epidemic spread. It is emphasised that deaths did not occur in immunised children. A similar report comes from Amsterdam (Ruys and Noordam). The M.R.C. report states neither the number or percentage of children immunised nor the relative incidence of diphtheria in immunised and non-immunised children, but the point is made that large numbers of immunised children contracted diphtheria. Most people will not be surprised at this result, when they note that in many of the cases in which the dosage of antigen is stated, the doses given were 0.1 c.c. and 0.3 c.c., of A.P.T. This minute dosage was accepted as entitling children to be described as "fully inoculated."

These adverse reports describe events occurring before 1942. This date is important as in that year a standard was set, under the Therapeutic Substances

Act, for diphtheria antigens. This required them to contain at least fifty Lf. units per c.c.; a high level of potency which compelled more than half of the makers in England to withdraw their products, temporarily, from the market (Holt, 1950). It was about this time, too, that Bousfield pointed out the necessity of an adequate first dose, at least 0.5 c.c. A.P.T., to give high and prolonged immunity, and also the enhancing effect on immunity of lengthening the time interval between doses of A.P.T. to at least four weeks. Since then diphtheria in England has been decreasing with increasing acceleration.

In Belfast, immunisation started in 1936. An extensive epidemic of diphtheria occurred in 1940 when only 15 per cent. of the child population had been immunisation. Dr. H. A. Warnock, then in charge of the immunisation scheme, was checking the effect of immunisation by Schick testing and by the incidence and severity of diphtheria in immunised children. By the end of 1940 he was convinced that the optimum first dose of A.P.T. was 0.5 c.c. From 1942, with increasing numbers of children immunised (now over 60 per cent.), the incidence of diphtheria in Belfast has continuously declined. In the period 1942 to 1950 there has been sixty-one deaths from diphtheria, all in non-immunised children. In fact, since 1945 there has been an increasing case mortality rate in non-immunised children. Many of the fatal cases were infected with the gravis strain of diphtheria bacillus. The presence of this strain in Belfast has not resulted in any increase in the incidence of diphtheria in the immunised.

While the advent of the gravis strain is usually an importation Professor J. W. McLeod of Leeds has postulated that it may arise by mutation from other strains of the diphtheria bacillus.

The striving after even better immunity has resulted in the production of a new antigen by Holt (Holt and Bousfield, 1949) called Purified Toxoid, Aluminium Phosphate precipitated (P.T.A.P.). This is a highly purified product in that practically all bacterial protein has been removed with the result that it very seldom causes local reactions. It has given even better Schick conversion rates than A.P.T., but it has been suggested that while it produces high antitoxic immunity it may not stimulate antibacterial immunity. This appears to be rather a fine point as the stimulation of bacterial antibodies can hardly be claimed for any diphtheria antigen all of which are essentially toxoids. P.T.A.P. has been used in the Belfast clinics for three years now, and children receiving it have not suffered any undue incidence of diphtheria when compared with their fellows who received A.P.T. over the same period.

Tetanus toxoid is in many respects a comparable antigen to diphtheria toxoid. During the last war it not only practically eliminated deaths from tetanus but also the symptoms of tetanus in the actively immunised wounded. Here, apparently, the need for antibacterial immunity does not arise. The improved diphtheria toxoids should reach the same high efficiency by means of proper dosage and spacing of doses.

The present system of immunisation is to give the first two doses at 9 and 10

months of age followed by a booster dose at 5 years. This leaves a possibility of some waning of immunity at 3 or 4 years of age. This might be overcome by delaying the second dose until six or nine months after the first. This long interval would, however, result in many second doses being overlooked.

Summary.

An association between inoculations and paralysis in poliomyelitis was not found in the 1950 epidemic in Belfast. The unusually high incidence of arm paralysis found elsewhere in inoculated children occurred in Belfast in non-inoculated children.

The use of a highly potent diphtheria antigen, such as P.T.A.P., properly administered, provides substantial protection against diphtheria even in the presence of the gravis type.

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